

Soft selective sweeps in evolutionary rescue

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ABSTRACT Evolutionary rescue occurs when a population that is declining in size because of an environmental change is rescued from extinction by genetic adaptation. Evolutionary rescue is an important phenomenon at the intersection of ecology and population genetics, and the study of evolutionary rescue is critical to understanding processes ranging from species conservation to the evolution of drug and pesticide resistance. While most population genetic models of evolutionary rescue focus on estimating the probability of rescue, we focus on whether one or more adaptive lineages contribute to evolutionary rescue. We find that when evolutionary rescue is likely, it is often driven by soft selective sweeps where multiple adaptive mutations spread through the population simultaneously. We give full analytic results for the probability of evolutionary rescue and the probability that evolutionary rescue occurs via soft selective sweeps. We expect that these results will find utility in understanding the genetic signatures associated with various evolutionary rescue scenarios in large populations, such as the evolution of drug resistance in viral, bacterial, or eukaryotic pathogens.

KEYWORDS adaptation; extinction; population density; genetic diversity; resistance evolution

2 **A**brupt environmental changes may lead to a demographic
3 decline in a population when the population is maladapted
4 to the new environment. This scenario necessitates an evolution-
5 ary response from the population if the population is to escape
6 extinction. The process by which genetic adaptation allows
7 a population to recover from the demographic consequences
8 of harsh environmental shifts has been termed “evolutionary
9 rescue”. Evolutionary rescue is a focus of many studies at the
10 interface of ecology and evolution in part due to recent attention to
11 climate change, drug resistance, pesticide resistance, and other
12 anthropogenic change of global and local environments (Gonzalez
13 *et al.* 2013; Alexander *et al.* 2014; Carlson *et al.* 2014). While
14 much attention has been given to theoretical and experimental
15 predictions regarding the probability that evolutionary rescue
16 occurs under various scenarios, we focus on the dynamics of
17 adaptive alleles and the associated genetic signatures left behind
18 by adaptation. More explicitly we are interested in how
19 selective sweeps that enable evolutionary rescue differ in the
20 number of ancestral backgrounds on which they emerge, based
21 on the conditions under which evolutionary rescue occurs. If
22 evolutionary rescue is facilitated by ‘hard’ selective sweeps—
23 wherein a single progenitor is responsible for the spread of the

24 beneficial variant—then genetic diversity will be removed from
25 the population as a result of adaptation as well as demographic
26 decline. By contrast, a population that adapts via ‘soft’ selec-
27 tive sweeps—wherein multiple ancestors have independently
28 derived beneficial variants—will preserve some of the ancestral
29 diversity that was present prior to the environmental shift
30 that caused the population to decline (Pennings and Hermisson
31 2006b).

32 Soft selective sweeps occur when adaptive alleles appear in
33 multiple individuals prior to sweeping through the population.
34 This leads to a sample genealogy that includes multiple adapted
35 ancestors in the new environment. The underlying criterium
36 for the occurrence of soft selective sweeps is that the presence
37 of adaptive mutations in the population is not a limiting factor
38 to the process of adaptation (Hermisson and Pennings 2005;
39 Pennings and Hermisson 2006a; Burke 2012; Messer and Petrov
40 2013). This criterium is fulfilled in many situations, such as
41 adaptation from previously neutral or deleterious standing genetic
42 variation (Hermisson and Pennings 2005), adaptation from
43 recurrent *de novo* mutation (Pennings and Hermisson 2006a) in
44 large populations. While soft selective sweeps appear to be
45 abundant in case studies of adaptation (Messer and Petrov 2013),
46 the signature of a soft selective sweep is crucially dependent on
47 the population sample and the underlying demographic history
48 of the population from which the sample is taken. Importantly,
49 many case studies of adaptation pertain to situations where the
50 demography of the population and the process of adaptation are

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necessarily interrelated. Particularly in the case of resistance evolution, beneficial mutations of large effect often confer benefits in terms of absolute fitness rather than relative fitness, thereby leading to demographic changes to the population. Previous work suggests that soft selective sweeps in populations with fluctuating population size can give rise to signatures of both hard and soft sweeps depending on when beneficial alleles arise, when they are sampled, and how advantageous they are (Wilson *et al.* 2014). However, in that work we had assumed that demography was independent of the allelic state at the locus under selection, an assumption that is valid only under models where fitness advantages are relative and density-independent (*e.g.* the standard Wright-Fisher model with selection or the Moran model). In this paper, we allow adaptation to influence demography. We explore a simple logistic model where fitness advantages are absolute and density-dependent within the context of an evolutionary rescue scenario. While most models of evolutionary rescue predict the probability that rescue occurs (Gomulkiewicz and Holt 1995; Orr and Unckless 2008; Uecker and Hermisson 2011; Martin *et al.* 2013; Orr and Unckless 2014; Uecker *et al.* 2014; Uecker and Hermisson 2015), we focus on the likelihood that rescue occurs via hard or soft sweeps.

The primary result of our analysis is that when rescue is likely to occur, it is more likely to occur via soft selective sweeps than hard selective sweeps. This result follows intuitively from the observation that the higher the time-averaged input of adaptive mutations, the greater is the probability of evolutionary rescue as well as the probability of soft selective sweeps. We demonstrate how our result is critically dependent on the population-scale mutation rate at the onset of the wildtype population decline and whether mutant growth rates are restricted by population density. We give analytical results for the probability of evolutionary rescue and the probability that rescue occurs via soft selective sweeps. We also give the waiting-time distributions for rescuing beneficial mutations. In the context of previous results connecting soft sweeps and post-adaptation genetic diversity, our results highlight a key correlation between genetic diversity following evolutionary rescue and the likelihood of evolutionary rescue (Feder *et al.* 2016).

Methods

Data availability

All code for the work performed in this article is available online at:

<https://github.com/benwilson87/evolutionary-rescue-soft-sweeps>

All plots were made using the ggplot2 (Wickham 2009) package in R (R Core Team 2015).

Simulations

Simulations were performed using a Gillespie algorithm (Gillespie 1976) programmed in Python (Python Software Foundation. Python Language Reference, version 2.7.6, available at <http://www.python.org>). All simulations began at the onset of the wildtype population decline. The wildtype population was initialized at a population size of 10^4 to be large enough to model the evolutionary processes by continuous approximations but small enough to be computationally efficient. For each round of simulation in the birth-death process, the algorithm used went as follows:

1. sample the waiting time t for an event from an exponential

distribution with rate parameter equal to the sum of all rates for all possible events beginning at time 0,

2. randomly assign a specific event according to the relative probabilities of occurrence of each type of event (*i.e.* mutation, wildtype birth/death, mutant birth/death),
3. and update the population and all event rates for the new time t .

The process was repeated until either 1) the population went extinct and no rescue occurred or 2) adaptation successfully rescued the population and the new mutant population reached 99% of its equilibrium size. Note that in simulations where rescue occurred, we did not necessarily wait until the mutant subpopulation reached fixation. This was done to model the effects of sampling the population when rescue would likely be suspected rather than when complete replacement of the wildtype population occurred, a feature that we believe to be more realistic. At the end of each simulation, the population composition was analyzed to determine if 1) no lineages existed following an extinction event, 2) only one mutant lineage existed indicating a hard selective sweep, or 3) more than one lineage existed indicating a soft selective sweep.

We simulated all combinations of:

1. five different wildtype decline rates: $\alpha \in \{0.01, 0.03, 0.1, 0.3, 1.0\}$,
2. three different mutation rates: $\mu \in \{10^{-5}, 10^{-4}, 10^{-3}\}$,
3. three different mutant birth rates: $b_m \in \{1.1, 1.3, 2.0\}$, and
4. two different population size limits: $K \in \{10000, 110000\}$

to encapsulate the extremes of the parameter range. For this particular range of α from 0.01 to 1.0, wildtype populations went extinct by approximately $\tau_{\text{end}} = \log(w_0)/\alpha$ which ranged from slow declines of length $\tau_{\text{end}} = 1000$ to extremely rapid declines of length $\tau_{\text{end}} = 10$ respectively. We restricted birth rates to be relatively small to prevent biologically unrealistic dynamics in the mutant population growth, however the absolute growth rates are potentially large at low population density. For all simulations, the wildtype and mutant death rates were set to 1. The population size limits were chosen to produce scenarios where the mutant would be unconditionally beneficial from the onset of the population decline ($K = 110000$) and where the mutant would initially suffer growth costs at high population density ($K = 10000$). Note that in the latter case, the mutant is actually deleterious with respect to the wildtype for all α except $\alpha = 1.0$, in which case the mutant and wildtype are initially identical in fitness. The parameter ranges were chosen to cover a wide range of phenomenon with combinations that produced extinction almost always and combinations that produced rescue via soft selective sweeps almost always.

Analysis

All mathematical analysis was numerically evaluated in Mathematica (Wolfram Research, Inc. 2010). In practice we found it neither necessary nor biologically meaningful to integrate to long times for all of our numerical integrations, so we chose to integrate to the time when a deterministically declining wildtype population would reach a single individual, $\tau_{\text{end}} = \log(w_0)/\alpha$, for our analytic calculations of P_{rescue} and P_{soft} . For the waiting-time distributions for τ_1 and τ_2 , we chose to integrate to the time when a deterministically declining wildtype population would reach 10% of its original size, $\tau_{\text{end}} = \log(w_0/1000)/\alpha$.

1 Results

2 We begin by modeling a population that is going extinct because
 3 of an environmental shift that leads to a demographic decline in
 4 the population (e.g. a drug enters the host environment of a virus
 5 causing the viral population to crash). We assume that mutants
 6 are not present at the onset of the population decline, i.e. there
 7 are no adaptive mutations present as standing genetic variation
 8 (e.g. because the adaptive mutations conferring drug resistance
 9 are highly deleterious in the absence of the drug). Adaptive mu-
 10 tations emerge on the background of the maladapted wildtype.
 11 We assume a single-locus, two-allele model where the mutation
 12 rate toward the beneficial state is μ and is constant in time. We
 13 assume back mutations to the wildtype state are negligible. Indi-
 14 viduals of the two types, maladapted wildtype (w) and adapted
 15 mutant (m), give birth or die with transition rates given by

- 16 • $w \rightarrow w + 1 : b_w w$
- 17 • $w \rightarrow w - 1 : d_w w$
- 18 • $m \rightarrow m + 1 : b_m m \left(1 - \frac{m+w}{K}\right)$
- 19 • $m \rightarrow m - 1 : d_m m$

20 where we assume $m + w < K$ so that mutant birth rates are
 21 strictly positive and biologically meaningful. The decline of
 22 the wildtype (maladapted) population is intrinsic to the geno-
 23 type and density-independent, i.e. the wildtype suffers de-
 24 creased reproductive success directly from its interaction with
 25 the environment and not from competition for shared resources.
 26 The wildtype population size can be deterministically approxi-
 27 mated by $w(t) = w_0 \exp(-\alpha t)$ where the variable α sets the rate
 28 at which the wildtype population declines and is equivalent
 29 to the absolute difference in per capita birth and death rates
 30 ($\alpha = d_w - b_w > 0$, in order to maintain the sign convention
 31 previously presented). It is worth noting that [Orr and Unckless](#)
 32 [\(2008\)](#) found the probability of evolutionary rescue to be approxi-
 33 mately two-fold higher for wildtype populations that experience
 34 logistic population regulation rather than strictly exponential de-
 35 cline in a previous model; however, we will focus strictly on the
 36 case of exponential decline for model simplicity. The carrying ca-
 37 pacity K sets the scale of density dependence and determines the
 38 equilibrium population size for the adapted population should
 39 adaptation occur: $m_{eq.} = K(1 - d_m/b_m)$, which is the value of
 40 m obtained by setting the mutant birth rate ($b_m m (1 - \frac{m+w}{K})$)
 41 equal to the mutant death rate ($d_m m$), setting $w = 0$, and solving
 42 for m assuming $b_m > d_m$.

43 For simplicity we will assume that $d_m = d_w$ such that the
 44 expected lifetime of each type is the same. In an alternative
 45 model, this assumption could be relaxed to investigate how
 46 genetic alterations to generation time or how different repro-
 47 ductive strategies (such as viral latency) could facilitate evolu-
 48 tionary rescue, but we will not explore these scenarios in this
 49 investigation. Ignoring the density-dependent scaling factor
 50 $1 - (m + w)/K$, the difference $b_m - b_w$ could be interpreted as
 51 the genotype-intrinsic growth advantage of a mutant individual
 52 over a wildtype individual. The parameter b_m also sets the maxi-
 53 mum per capita birth rate for mutants at low population density.
 54 For our model, we do not consider extremely large birth rates
 55 ($b_m \gg 1$) to avoid extreme jumps in the population size over
 56 short timescales. Note that this model is closely analogous to
 57 scenario 2 under *Alternative Forms of Population Regulation* in [Orr](#)
 58 [and Unckless \(2008\)](#) except that our model is in continuous time
 59 rather than discrete time. Our model is also similar to the $D = 1$
 60 panmictic model presented in [Uecker et al. \(2014\)](#) except that we
 61 exclude the contribution of standing genetic variation and again

62 look at continuous time versus discrete time.

63 At any given time t , mutations occur at a rate $w(t)\mu$ and
 64 establish with a probability $p_{est.}(t)$. Establishment occurs when
 65 a mutation survives extinction due to drift at low copy number.
 66 From analysis of soft sweeps via *de novo* mutation in populations
 67 of constant size, we know that soft sweeps are only expected
 68 to occur when $w_0\mu \sim 1$ or greater ([Pennings and Hermisson](#)
 69 [2006a](#)). In most scenarios we consider, we correspondingly scale
 70 μ to be either $1/w_0$ or $10/w_0$ to ensure that mutations occur
 71 frequently enough at the beginning of the environmental shift
 72 to expect multiple adaptive lineages to appear during the rescue
 73 scenario, though their survival will ultimately depend on the
 74 other parameters previously described, namely the carrying
 75 capacity (K), the wildtype decline rate (α), and the mutant birth
 76 rate (b_m). Note that the decline in the wildtype population means
 77 that adaptation will eventually be mutation-limited in all cases,
 78 i.e., the supply rate of mutations will always go to zero as the
 79 wildtype population goes extinct. We also consider situations
 80 where adaptation is likely to only proceed via hard sweeps (if at
 81 all) ($w_0\mu < 1$) to illustrate the limitations of our results. Figure 1
 82 gives an illustration of the rescue scenario.

83 **The time-dependent probability of establishment**

We can derive the probability of establishment for a mutation
 arising at a particular time τ using the methodology presented
 in [Uecker and Hermisson \(2011\)](#) (see specifically equation A5 un-
 der *Fixation in General Ecological Models* in the appendix and equa-
 tion 16a in the main text as well as [Allen \(2010\)](#) pages 278–280
 for the general theory). [Uecker and Hermisson \(2011\)](#) showed
 that for a time-inhomogeneous birth-death process (such as the
 specific birth-death model presented here) we can write the proba-
 bility of establishment for a single mutant starting at particular
 time $\tau = 0$ in terms of the total per capita mutant birth rate $B(t)$
 and total per capita mutant death rate $D(t)$. The general result
 takes the form

$$p_{est.} = \frac{2}{1 + \int_0^\infty (B(t) + D(t)) \exp\left(-\int_0^t (B(t') - D(t')) dt'\right) dt}$$

84 where t' is a dummy variable for the nested integral. For our
 85 specific birth-death model, $B(t) = b_m \left(1 - \frac{w(t)}{K}\right)$ and $D(t) = d_m$
 86 can be taken directly from the transition rates presented at the
 87 beginning of this section, and the probability of establishment
 88 for a single mutant appearing at a particular time τ is given by

$$p_{est.}(\tau) = \frac{2}{1 + \int_0^\infty \left(b_m \left(1 - \frac{w(t+\tau)}{K}\right) + d_m\right) \exp\left(-\int_0^t \left(b_m \left(1 - \frac{w(t'+\tau)}{K}\right) - d_m\right) dt'\right) dt} \quad (1)$$

89 where the instantaneous time τ now appears explicitly because
 90 τ is not fixed at zero.

91 Note that we have neglected the mutant population size in
 92 the density-dependent terms under the assumption that mutant
 93 lineages have independent probabilities of establishment while
 94 the mutant population size is low and while the expected time
 95 between successive establishments is short. Later we will show
 96 that this assumption breaks down for rescue scenarios with
 97 slow decline rates and when the expected time between mutant
 98 establishment increases.

99 **The role of population density**

100 We demonstrate here how population density influences the pro-
 101 cess of evolutionary rescue in our model. Note that population
 102 density is the population size relative to the carrying capacity,

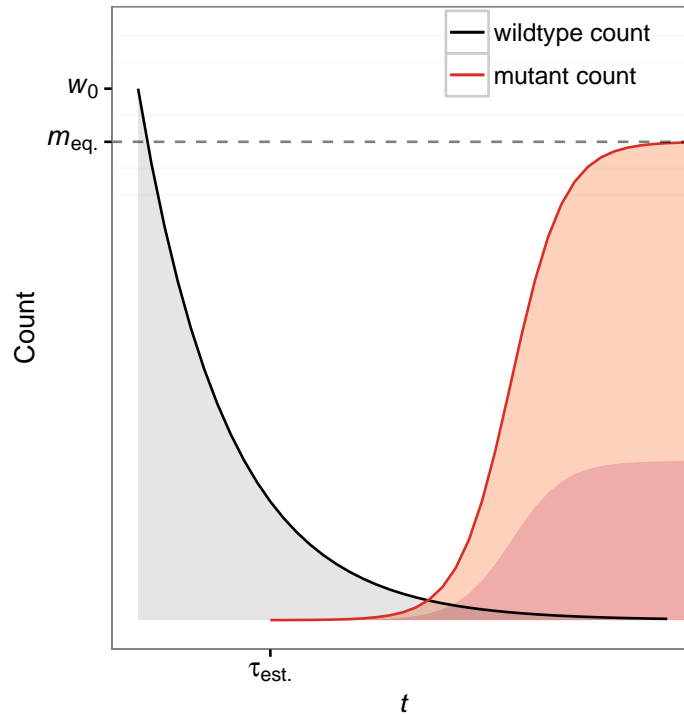


Figure 1 Model depiction of evolutionary rescue. A population initially composed of maladapted wildtype individuals (black line) declines exponentially from its original size w_0 following an environmental shift. A beneficial mutation appears on the background of a wildtype individual and establishes at time $\tau_{\text{est.}}$, at which point the population is destined to be rescued via adaptation. If a mutant fails to establish before the wildtype population goes extinct, then no rescue occurs. Following rescue, the mutant population (red line) will equilibrate at a new population size $m_{\text{eq.}} = K(1 - d_m/b_m)$. In some cases of rescue, multiple mutant lineages can establish before the wildtype population goes extinct, leading to a soft selective sweep as illustrated by the multiple shaded lineages (red shading) within the mutant population (red line).

not the population size itself. Including density dependence through a carrying capacity K ensures that a rescued population reaches an equilibrium size at long timescales. Population density also has critical effects on mutant establishment because it determines the growth rate of the mutant through time.

We can separate the effects of population density into two characteristics: the growth rate of the mutant at the onset of the wildtype population decline and the rate at which density-dependent growth restriction decays over time. The initial growth rate of the mutant depends on the ratio of the starting wildtype population size to the total population size limit (w_0/K). If the initial population density is high ($w_0/K > 1 - d_m/b_m$), *i.e.* the wildtype population size is similar to the carrying capacity, then the birth rate of the mutant may (initially) be lower than its death rate, making it unlikely that a mutant establishes.

By contrast, in situations where the carrying capacity is much larger than the wildtype population size ($w_0/K < 1 - d_m/b_m$), a mutant lineage that appears at the onset of the wildtype population decline will have a net positive growth rate from the onset. In other words, early mutants have less chance of surviving when initial density is higher.

The rate of decline of the wildtype population determines how quickly mutant growth rates increase. Scenarios with fast wildtype population decline will alleviate mutant growth restrictions more quickly and increase the probability of establishment (conditional on appearance), although fast wildtype population decline will also decrease the rate at which mutants appear. We highlight these different aspects of density dependence in our model because we find it important to note that 1) early mutants are not unconditionally advantageous compared to wildtype individuals, and 2) the probability of establishment is intrinsically tied to the wildtype population decline. While this first point arises mathematically from our assumption of wildtype population decline being density-independent, we retain it as a mathematical convenience in order to model a mutant fitness trade-off between rapid growth at low population density and weak competitive ability at high population density without the addition of another model parameter.

The influence of population density on $p_{\text{est.}}(t)$ can be seen by comparing values of $p_{\text{est.}}(t)$ between situations of high and low population density at the onset of the wildtype population decline, as illustrated in Figure 2A. In the scenario with high population density ($w_0/K > 1 - d_m/b_m$), $p_{\text{est.}}(t)$ is essentially zero until the wildtype population has declined sufficiently to give mutants a positive growth rate (bottom, red line). This growth rate transition occurs at $w(t) = w^* = K(1 - d_m/b_m)$. Using the deterministic approximation to the wildtype population size, we can estimate that this transition occurs at

$$t^* \sim -\frac{1}{\alpha} \log \left(\frac{K(1 - d_m/b_m)}{w_0} \right) \quad (2)$$

by setting $w(t) = w^* = K(1 - d_m/b_m)$, and solving for t . By contrast, the scenario with low population density at the onset ($w_0/K < 1 - d_m/b_m$) shows that beneficial mutants have an appreciable probability of establishing from the beginning of the environmental shift (top, blue line). Note that because the probability of establishment is measured for a mutation occurring at time τ and because the density restriction imposed by the wildtype population declines monotonically with time, $p_{\text{est.}}$ will increase monotonically with time in our model. It asymptotes at

a value

$$p_\infty = \frac{b_m - d_m}{b_m} \quad (3)$$

that is obtained by taking the limit as $\tau \rightarrow \infty$ for Equation (1) and is therefore independent of K and α because the wildtype population will eventually go extinct. When we set $d_m = 1$, and when the mutant birth rate is not much higher than 1, we find that the fixation probability is approximately $b_m - 1$ which is equivalent to s in a constant population size model or $s + r$ in a growing population. The reason we don't recover the classic $p_{\text{est.}} \approx 2s$ result from Haldane (1927) or the $2(s + r)$ result from Otto and Whitlock (1997) is that in our model (with $d_m = 1$ and $b_m = 1 + s$ and s small), the variance in offspring number is twice what it is in a Wright-Fisher model, which means that the fixation probability is half of what it is in a Wright-Fisher model.

Although the probability of establishment increases over time, the rate of appearance of mutants ($w(t)\mu$) decreases over time, coinciding with the wildtype population size decline. Thus, the total rate of successful beneficial mutants, $R(t) = w(t)\mu p_{\text{est.}}(t)$, will eventually decay as shown in Figure 2B). In the following section, we show how $R(t)$ can be used as the intensity function for a time-inhomogeneous Poisson process that determines mutant establishments.

Evolutionary rescue via soft selective sweeps

With these model considerations in mind, we can derive the probability that a population headed for extinction is rescued by at least one successful adaptive mutant. If we model mutant establishments using a time-inhomogeneous Poisson process with rate parameter Λ , the general form of the probability that k mutants establish is $P(K = k) = \Lambda^k \exp(-\Lambda)/k!$ assuming independence. For our model the rate parameter is derived by integrating the intensity function $R(t) = w(t)\mu p_{\text{est.}}(t)$ over all time. The probability of rescue is $1 - P_{\text{extinction}}$, or one minus the probability that no mutants establish ($k = 0$). The probability that no mutants establish is $\exp(-\int_0^\infty R(t)dt)$. This leads to a total probability of rescue equal to

$$P_{\text{rescue}} = 1 - \exp \left(-\int_0^{\tau_{\text{end}}} R(t)dt \right) \quad (4)$$

where we have replaced the upper limit ∞ with $\tau_{\text{end}} = \log(w_0)/\alpha$ representing the time it would take for a deterministically declining wildtype population to reach a single individual. Note that this is the same result as obtained by Uecker and Hermisson (2011) in Equation A7. The integral in Equation (4) is the area under the intensity function depicted in Figure 2B and represents the number of mutants expected to establish during the time when mutations can occur in wildtype individuals.

Assuming independence between mutant lineages, we can gain an overall picture of whether rescue is more likely to occur via hard or soft selective sweeps using the same time-inhomogeneous Poisson process to model the establishment of each individual lineage. To determine the probability of evolutionary rescue via soft selective sweeps, we will first want to calculate that the probability that only one mutant establishes ($k = 1$) before the wildtype population goes extinct, *i.e.* evolutionary rescue occurs via a hard selective sweep. This is given by

$$P_{\text{hard}} = \left(\int_0^{\tau_{\text{end}}} R(t)dt \right) \exp \left(-\int_0^{\tau_{\text{end}}} R(t)dt \right). \quad (5)$$

Evolutionary rescue requires at least one mutant lineage to establish before the wildtype population goes extinct, and all evolutionary rescue that does not occur via a hard sweep must

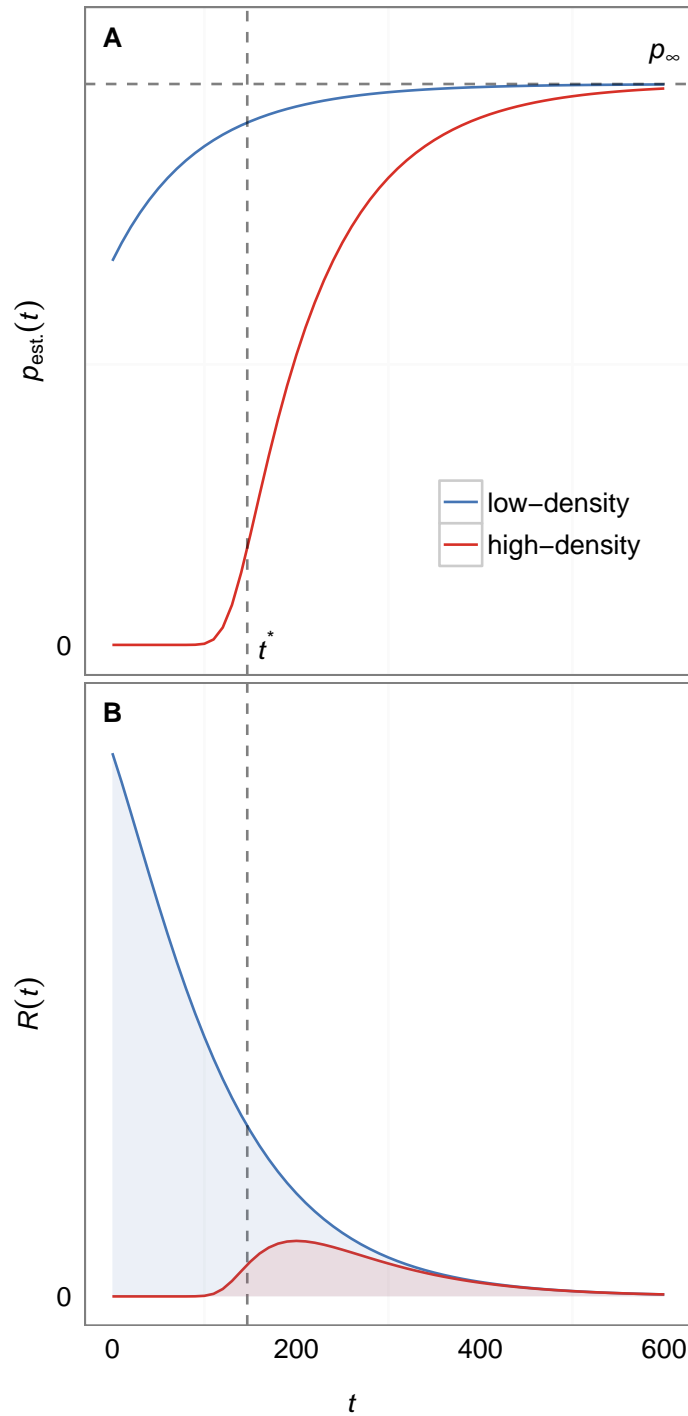


Figure 2 Establishment probability and intensity function distributions. Part A shows the establishment probability distributions for mutations appearing at time t in low- (top, blue) and high-density (bottom, red) scenarios with all parameters being equal except for K . For low-density scenarios, the probability of establishment increases monotonically as the density restriction on mutant growth declines to zero with the wildtype population. For high-density scenarios, the probability of establishment is essentially zero until the wildtype population declines to a size w^* at t^* (see Equation (2)) whereupon it will increase monotonically just as in the low-density scenario (these approximations can be conservative). Note that both low- and high-density scenarios have distributions that asymptote to the same value, p_{∞} , because p_{∞} is only dependent on the unscaled per capita birth and death rates of the mutant (see Equation (3)). Part B shows the distributions for the corresponding intensity functions $R(t) = w(t)\mu p_{\text{est.}}(t)$ for the same two scenarios in Part A. $R(t)$ gives the instantaneous rate at which mutants successfully establish and save the population from extinction. $R(t)$ eventually declines to zero with the wildtype population size (see Figure 1) even though the establishment probability increases with time. The shaded area under $R(t)$ determines the probability of evolutionary rescue and is generally larger in low-density (top, blue) scenarios than in high-density scenarios (bottom, red).

1 occur via a soft sweep by definition. Therefore, the probability
2 of evolutionary rescue via soft selective sweeps is

$$P_{\text{soft}} = P_{\text{rescue}} - P_{\text{hard}}. \quad (6)$$

3 To confirm our analysis, we performed forward-time birth-
4 death simulations in populations initially composed of 10,000
5 wildtype individuals over multiple values of K , α , b_m , and μ
6 (see Methods section for details). If we examine P_{rescue} for
7 low-density ($w_0 = 10,000$, $K = 110,000$) and high-density
8 ($w_0 = 10,000$, $K = 10,000$) rescue scenarios, we can see that
9 the overall probabilities of rescue and rescue via soft sweeps
10 decline with increasing α (see simulation and analytic values
11 from Equation (4) and Equation (6) plotted in Figure 3 and Fig-
12 ure 4). The qualitative dependence on decline rate in our model
13 is the same as seen in previous models where mutation was
14 weak (Orr and Unckless 2008, 2014). As for the other relevant pa-
15 rameters in our model, the probabilities of evolutionary rescue
16 and rescue via soft sweeps increase universally with increasing
17 μ and b_m . Rescue is generally higher in low-density scenarios
18 (when the carrying capacity is higher than the wildtype popu-
19 lation size) than in high-density scenarios (when the carrying
20 capacity is close to the wildtype population size), similar to sim-
21 ulation results for scenario 2 under *Alternative Forms of Population*
22 *Regulation* in Orr and Unckless (2008). We also find that sweeps
23 are generally softer in low-density scenarios than in high-density
24 scenarios.

25 Simulations and analysis agree well for both low- and high-
26 density scenarios when comparing corresponding values of
27 P_{rescue} . Our analysis also agrees with the observed probabil-
28 ity of rescue via soft sweeps in scenarios where mutation is high
29 and mutants have appreciable chance of establishment (see Fig-
30 ure 3 and Figure 4). In instances where mutation is rare (such as
31 when $w_0\mu < 1$ for low-density rescue or when the population
32 must decline dramatically before mutants can establish such that
33 $w^*\mu < 1$ for high-density rescue) and where the wildtype pop-
34 ulation declines slowly, our analytic assumption regarding the
35 independence of mutant lineages during establishment breaks
36 down resulting in deviations from the values observed in simu-
37 lations. In particular, our analysis overestimates the probability
38 of soft sweeps because it excludes the contribution of the mutant
39 subpopulation in the density-dependent term in Equation (1).
40 See *Evolutionary rescue via hard selective sweeps* for further
41 explanation.

42 **Simple Poisson approximation for low-density rescue**

43 From Equation (3) follows that, when $d_m = 1$, and when the
44 mutant birth rate is not much higher than 1, the establishment
45 probability asymptotes to $b_m - 1$. As can be seen in Figure 2A,
46 when the population density is low, this asymptote is reached
47 quickly. It is therefore possible to derive a simple approxima-
48 tion under the assumption that $p_{\text{est.}} = b_m - 1$, independent
49 of t . When the initial wildtype population size is w_0 and the
50 wildtype population declines at rate α , then the total number of
51 individuals in the population until extinction is expected to be
52 w_0/α . If we multiply this with the mutation rate and the estab-
53 lishment probability, we find the expected number of successful
54 mutants to be $k = (w_0\mu/\alpha)(b_m - 1)$. Under the assumption that
55 mutations are independent, the realized number of successful
56 mutants will follow a Poisson distribution with rate parameter

$$\Lambda = \frac{w_0\mu(b_m - 1)}{\alpha} \quad (7)$$

57 Because Λ is equal to the expected value for Poisson random
58 variables, it is easy to see from this relationship that the ex-
59 pected number of beneficial mutants that survive extinction
60 increases with increasing $w_0\mu$ and b_m and decreases with in-
61 creasing α . This approximation is illustrated in Figure 3 and
62 generally gives slight overestimates to the probabilities of res-
63 cued ($P_{\text{rescue}} = P(k \geq 2)$) and rescue via soft sweeps ($P_{\text{soft}} =$
64 $P(k \geq 1)$) seen in simulations, which is expected because the
65 approximation uses the highest establishment probability for all
66 t .

67 **Soft sweeps are more likely when rescue is likely**

68 Both P_{rescue} and P_{soft} vary similarly with the underlying pa-
69 rameters of our model because they both strongly depend on
70 the area under the intensity function $R(t)$. If we ask whether
71 sweeps are more likely to be soft conditional on rescue occur-
72 ring, we can thus see an obvious correlation between the two
73 phenomena. This correlation is shown in Figure 5 where
74 $P_{\text{soft}}|P_{\text{rescue}}$ is plotted against P_{rescue} . Mathematically, we can de-
75 rive the relationship using Equation (4), Equation (5), and Equa-
76 tion (6). First, solving P_{hard} in terms of P_{rescue} yields $P_{\text{hard}} =$
77 $-(1 - P_{\text{rescue}})\log(1 - P_{\text{rescue}})$. Solving for $P_{\text{soft}}|P_{\text{rescue}}$ in terms
78 of P_{rescue} then gives

$$\begin{aligned} P_{\text{soft}}|P_{\text{rescue}} &= P_{\text{soft}}/P_{\text{rescue}} \\ &= (P_{\text{rescue}} - P_{\text{hard}})/P_{\text{rescue}} \\ &= (P_{\text{rescue}} + (1 - P_{\text{rescue}})\log(1 - P_{\text{rescue}}))/P_{\text{rescue}} \\ &= 1 + \left(\frac{1 - P_{\text{rescue}}}{P_{\text{rescue}}}\right)\log(1 - P_{\text{rescue}}) \end{aligned} \quad (8)$$

79 which is monotonically increasing for P_{rescue} in $(0, 1)$.

80 While it may be intuitive that the probabilities of rescue and
81 soft sweeps are correlated (both the probability of rescue and the
82 probability of soft sweeps depend on the same rate parameter
83 and increase with the number of mutations that occur), we high-
84 light it because of its relevance to post-rescue genetic diversity.
85 The hallmark of a soft selective sweep is that multiple lineages
86 are preserved after selection (Hermisson and Pennings 2005;
87 Pennings and Hermisson 2006a). This means that selection need
88 not remove all genetic diversity in a population following evolu-
89 tionary rescue, especially when rescue is expected to be common.
90 We discuss why this might be important in the Discussion.

91 **Evolutionary rescue via hard selective sweeps**

92 Although the primary focus of this paper is to investigate soft
93 selective sweeps in evolutionary rescue, we feel that evolution-
94 ary rescue via hard sweeps deserves special attention. When
95 mutations are rare, the population will typically either go extinct
96 or be rescued by a single mutant lineage via a hard selective
97 sweep. Neither of these outcomes should impact the validity
98 of our assumption of independence between lineages in Equa-
99 tion (1) because they involve either zero or one mutant lineages
100 respectively. However, in scenarios where the wildtype popula-
101 tion declines very slowly and where the time between mutant
102 establishments is long, it is possible that one mutant lineage
103 establishes and reaches a size large enough to prevent a second
104 mutant lineage from establishing, leading to a hard sweep. This
105 scenario is not accounted for in our analysis because we exclude
106 the mutant contribution to population density in the density-
107 dependent term in Equation (1). In these situations the window
108 of opportunity for a second mutant lineage to establish is limited
109 by the time it takes for the first established mutant lineage to

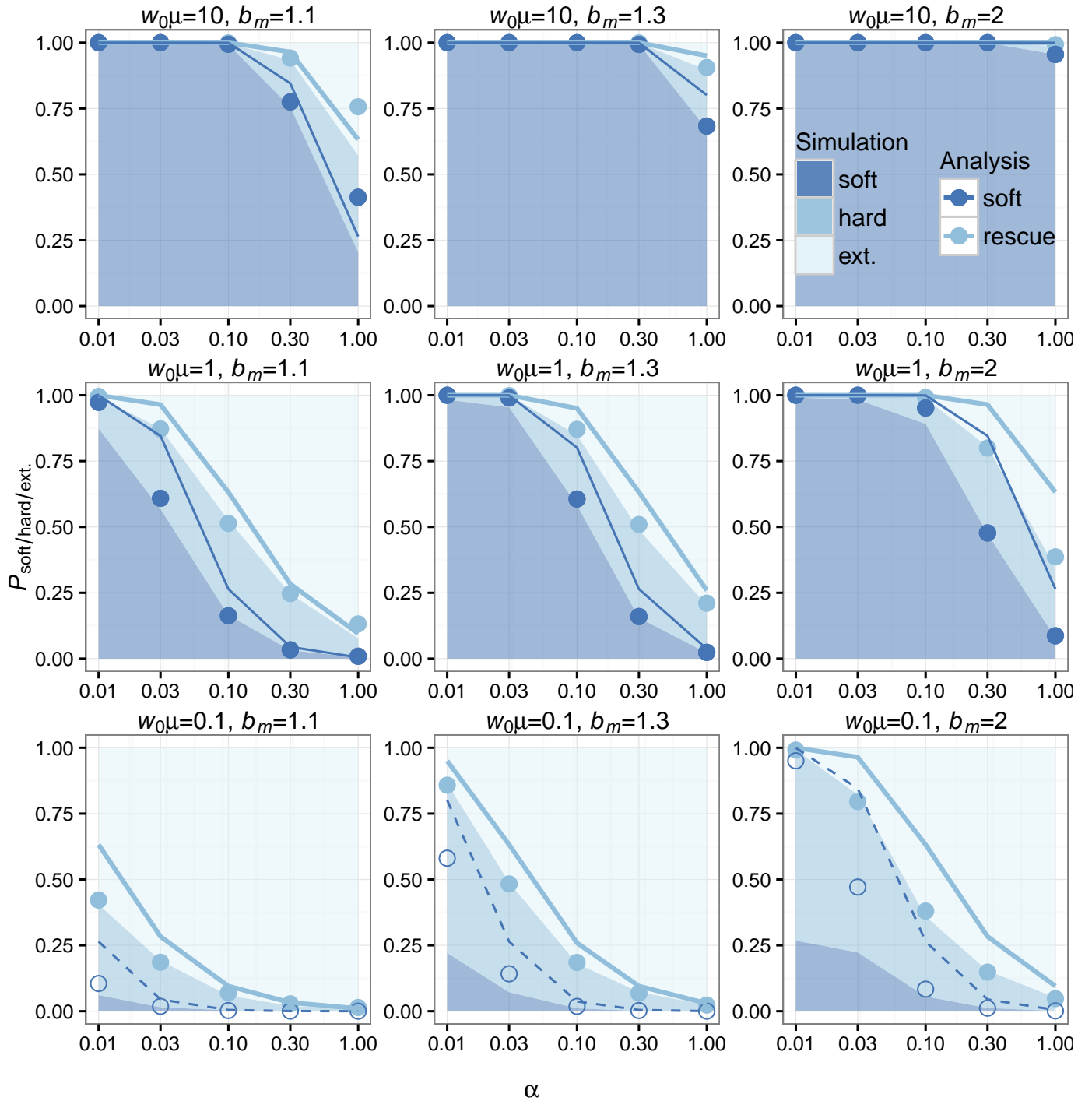


Figure 3 Simulations and analytic predictions for evolutionary rescue in low-density scenarios. The probabilities of observing rescue via soft selective sweeps, rescue via hard selective sweeps, or extinction as a function of the decline rate α (logarithmic scale) measured over 1000 simulations (see Methods) for each combination of model parameters are indicated as stacked bar plots. The color key indicates shading for simulation outcomes. Population-scale mutation rate increases between plots from bottom to top, and unscaled per capita mutant birth rate increases between plots from left to right. The analytic predictions for each parameter combination show P_{soft} (bottom blue points) and $P_{\text{rescue}} = P_{\text{hard}} + P_{\text{soft}}$ (top, light blue points). Our Poisson approximation is indicated using lines of the same colors. For analytic predictions and our Poisson approximation of P_{soft} , points where $w_0\mu \geq 1$ are shaded and lines are solid. Our analysis has high concordance with the observed probability of rescue for each parameter combination. Our analysis also has high concordance with the observed probability of rescue via soft sweeps for most parameter combinations, except in instances where our independence assumption breaks down ($w_0\mu < 1$) for low decline rates (bottom row, leftmost α values).

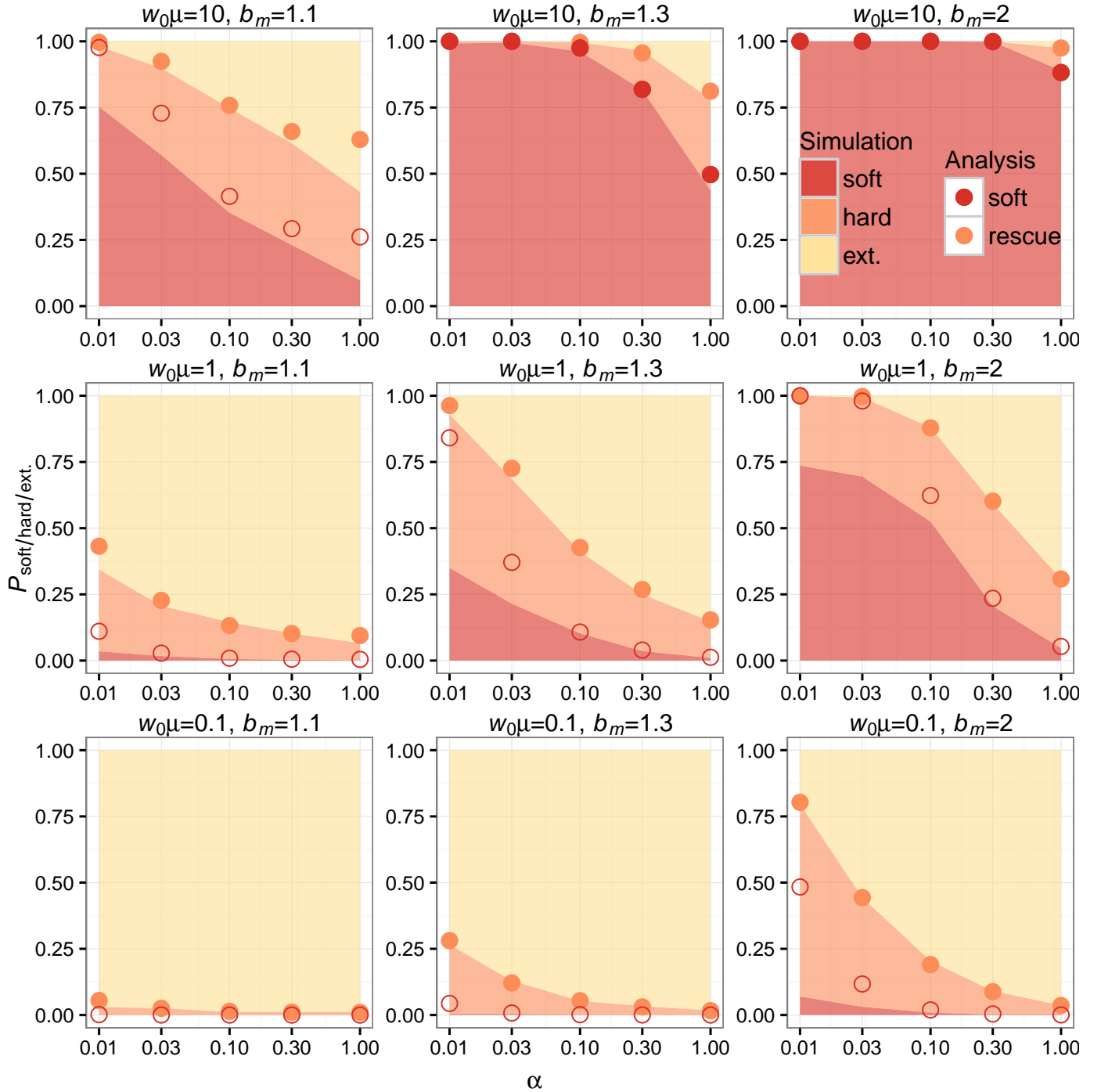


Figure 4 Simulations and analytic predictions for evolutionary rescue in high-density scenarios. The probabilities of observing rescue via soft selective sweeps, rescue via hard selective sweeps, or extinction as a function of the decline rate α (logarithmic scale) measured over 1000 simulations (see Methods) for each combination of model parameters are indicated as stacked bar plots. The color key indicates shading for simulation outcomes. Population-scale mutation rate increases between plots from bottom to top, and unscaled per capita mutant birth rate increases between plots from left to right. The analytic predictions for each parameter combination show P_{soft} (bottom red points) and $P_{\text{rescue}} = P_{\text{hard}} + P_{\text{soft}}$ (top orange points). For analytic predictions of P_{soft} , points where adaptation $w^*\mu \geq 1$ are shaded. Our analysis has high concordance with the observed probability of rescue for each parameter combination. As in the low-density scenario, our analysis has good concordance with the observed probability of rescue via soft sweeps for most parameter combinations, except in instances where our independence assumption breaks down ($w^*\mu < 1$) and for low decline rates (bottom and middle rows, leftmost α values). Evolutionary rescue is less likely for more parameter combinations in the high-density scenario because the wildtype population must decline before establishment of mutants is likely (see Figure 2).

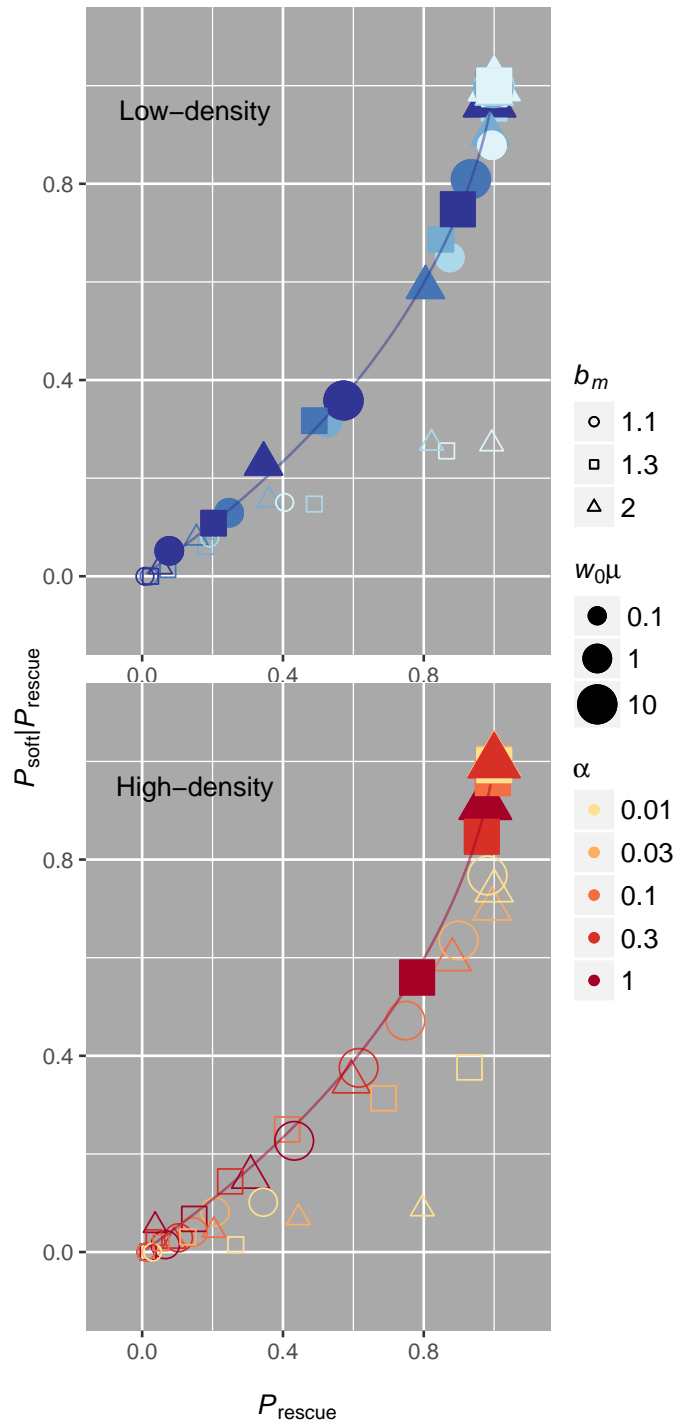


Figure 5 When rescue is likely it is driven by soft sweeps. Both in low-density (top, blue) and high-density (bottom, red) scenarios, simulations (points) indicate that soft sweeps are more prevalent when evolutionary rescue is likely. The correlation lines assume independence between lineages and are plotted according to the relationship in Equation (8). We have only shaded simulations where our independence assumption is valid ($w_0\mu \geq 1$ in low-density rescue and $w^*\mu \geq 1$ in high-density rescue, where $w^* = K(1 - d_m/b_m)$). When mutation is rare, we expect our modeling assumptions to fail or soft sweeps to be unlikely. Departures from independence are more pervasive in high-density situations, especially when decline rates are slow.

bring the total population size high enough to substantially decrease the establishment probability of a second mutant lineage, assuming the wildtype population declines slowly enough to allow multiple mutations to appear before it goes extinct. This is similar to the scenario in [Pennings and Hermisson \(2006a\)](#) where a second mutant establishing was limited by the time it takes the first mutant to sweep in a population. What is most noteworthy about these situations is that whether evolutionary rescue occurs via soft sweeps or not, depends not only on the population-scale mutation rate at the onset of the environmental shift but also on the population density at that point in time. Departures from our independence assumption are more frequent in the high-density scenarios than in the low-density scenarios that we explored. This is because in high-density scenarios, mutant lineages are unlikely to establish until the wildtype population declines to $w^* \sim K(1 - d_m/b_m)$, at which point the population-scale mutation rate can be small ($w^*\mu < 1$) even when the initial population-scale mutation rate was large ($w_0\mu \geq 1$). Understanding when we expect non-independence and when we expect evolutionary rescue to appear via soft sweeps is therefore dependent on approximating the population-scale mutation rate when mutant lineages have an appreciable probability of establishing. We have distinguished scenarios where mutant establishment probabilities are approximately independent ($w_0\mu \geq 1$ in low-density rescue and $w^*\mu \geq 1$ in high-density rescue) from scenarios where our assumptions regarding independence between lineages are expected to break down ($w_0\mu < 1$ in low-density rescue and $w^*\mu < 1$ in high-density rescue) in [Figure 3](#) and [Figure 4](#). While this heuristic distinction is conservative and does not account for differences in decline rate, we find that it provides a clean partition of where our analysis performs well (shaded points in [Figure 3](#) and [Figure 4](#)) and where it does not (open points in [Figure 3](#) and [Figure 4](#)).

Waiting-time distributions for the establishment of mutants

It may be of interest to reformulate the results from our previous analysis in terms of the waiting times associated with the establishment of the individual adaptive lineages during the extinction process. As in the previous analysis, we will assume independence between mutant lineages. Under this assumption, we define τ_1 to be the waiting time for the first mutant lineage to establish. τ_1 has probability density equal to

$$p(\tau_1) = R(\tau_1)\exp\left(-\int_0^{\tau_1} R(t)dt\right) \quad (9)$$

conditional on evolutionary rescue occurring. Note that this is identical to Equation A8 in [Uecker and Hermisson \(2011\)](#) with $P_{\text{rescue}} = 1$. Conditional on the establishment of a first adaptive mutant at τ_1 , the probability density for the establishment of a second adaptive mutant at time τ_2 takes the same form integrated over all possible τ_1 . The probability density for τ_2 is

$$p(\tau_2) = \int_0^{\tau_2} p(\tau_1)R(\tau_2)\exp\left(-\int_{\tau_1}^{\tau_2} R(t)dt\right) d\tau_1. \quad (10)$$

Distributions for both τ_1 and τ_2 are plotted for one set of parameters in [Figure 6](#). Equation (9) and Equation (10) are in good agreement with forward-time birth-death simulations for this parameter combination, although it is important to consider the previous discussion regarding the independence of mutant lineages during establishment and the regime where independence breaks down, in which case we expect departures for the

distribution for τ_2 but the distribution for τ_1 should remain unchanged. In theory, we could use the probability density of τ_1 to approximate a trajectory $m(\tau_1)$ for the first established mutant that could then be used to calculate an establishment probability for a second mutant that includes the previous mutant's contribution to population density. However, we find this to be unnecessarily convoluted in practice.

Discussion

We show that adaptation often proceeds via soft selective sweeps when evolutionary rescue is likely. Our results regarding the probability of evolutionary rescue agree with results previously published using similar models of adaptation under *de novo* mutation variation ([Orr and Unckless 2008](#); [Uecker and Hermisson 2011](#); [Martin et al. 2013](#); [Orr and Unckless 2014](#); [Uecker et al. 2014](#)).

The generality of soft sweeps in evolutionary rescue

We study soft selective sweeps via *de novo* mutation as a mode of evolutionary rescue because of their relevance to case studies of adaptation and particularly adaptation to strong environmental pressures ([Karasov et al. 2010](#); [Messer and Petrov 2013](#); [Pennings et al. 2014](#); [Feder et al. 2016](#)). While adaptation from standing genetic variation is also expected to generate soft sweeps ([Hermisson and Pennings 2005](#)), it may be the case that adaptive mutants are absent at the onset of an environmental shift because they are strongly deleterious in the prior environment, as can be the case in resistance evolution ([Andersson 2003](#); [Shi et al. 2004](#); [Cong et al. 2007](#)). In reality, both modes of adaptation will play a role in the process of evolutionary rescue, and evolutionary rescue will depend strongly on the underlying ecological and population genetic factors of the adapting population such as population density, population substructure, epistasis, and genetic recombination. For example, whether fast decline of maladapted individuals in the population inhibits or facilitates evolutionary rescue depends strongly on whether adaptive mutations already exist in the population and whether there is strong population substructure ([Wargo et al. 2007](#); [Gatenby et al. 2009](#); [Read et al. 2011](#); [Uecker et al. 2014](#)). Even in unstructured populations, fast decline of the wildtype population can increase the probability of rescue from standing genetic variation while decreasing the probability of rescue from *de novo* mutation, leading to a nonmonotonic dependence on decline rate when both adaptive processes are present (see Appendix B in [Uecker et al. \(2014\)](#)). And whether complex adaptations that require multiple mutations facilitate evolutionary rescue when a population faces an environmental challenge is strongly dependent on epistatic interactions between mutations and the presence (or absence) of genetic recombination ([Lindsey et al. 2013](#); [Uecker and Hermisson 2015](#)). Nevertheless, modeling evolutionary rescue as a Poisson process in each of these complex scenarios has led to a general form for the probability of rescue as $P_{\text{rescue}} = 1 - \exp(-\Lambda)$, where Λ is the number of expected mutants generated via *de novo* mutation or existing in standing variation that are expected to survive extinction. While this number is a complex function of the aforementioned ecological and population genetic factors, the probability is nonetheless always higher when the number of surviving mutants is higher. Our choice of a *de novo* mutation model in this paper, while simple, is meant to illustrate this without unnecessary complications. Previous empirical observation ([Bell and Gonzalez 2009](#)) and intuition therefore suggest that when rescue is likely, more adap-

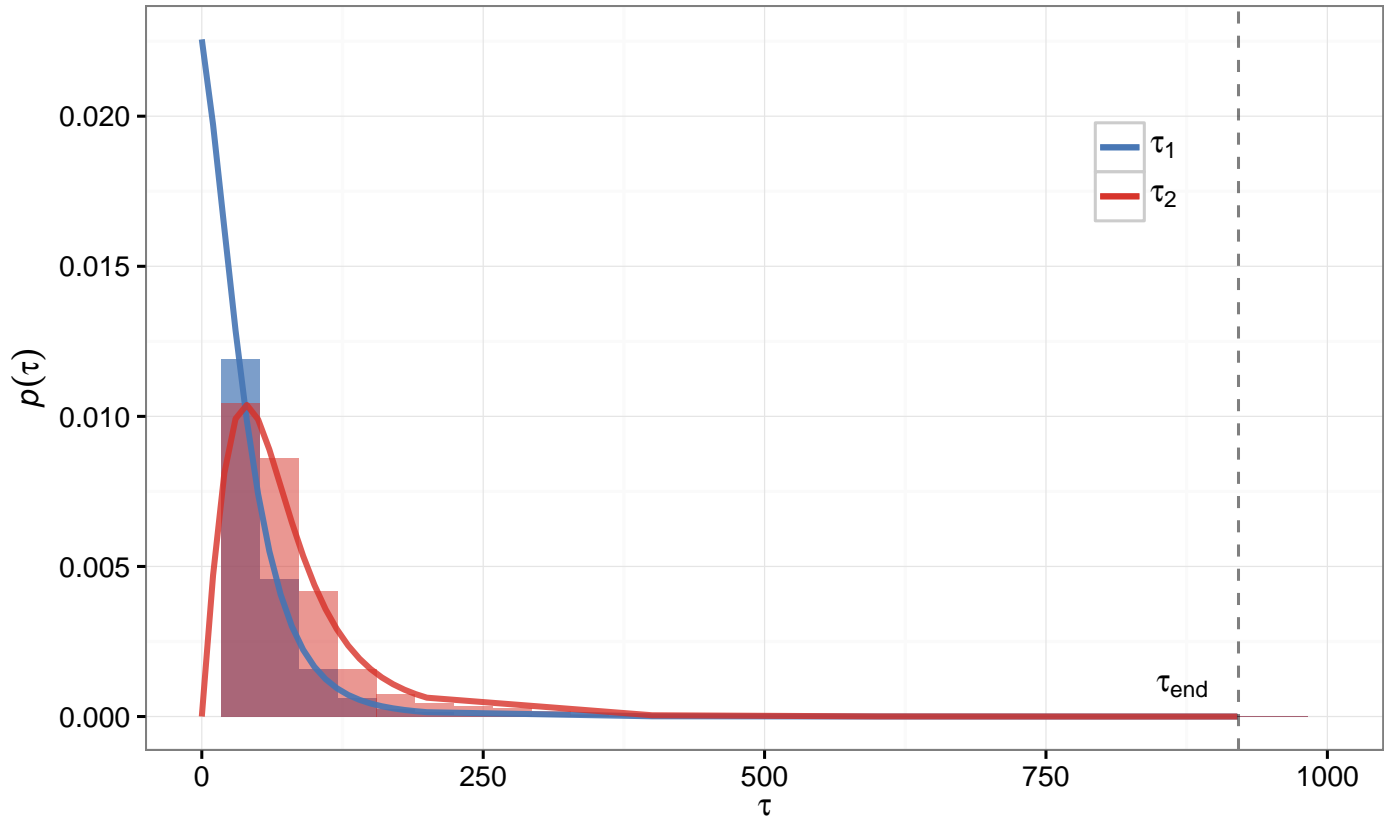


Figure 6 Waiting-time distributions for the establishment of the first and second mutants during rescue. Shown are the probability densities for the first and second mutants to establish during evolutionary rescue according to Equation (9) (blue line) and Equation (10) (red line). Empirical distributions from 10,000 simulations are shown in the same corresponding colors but as density histograms. The particular scenario is a low-density rescue scenario with $w_0 = 10,000$, $K = 110,000$, $\alpha = 0.01$, $b_m = 1.1$, and $w_0\mu = 1$.

1 tive mutants are expected to be involved. It is for this reason that
2 we expect soft sweeps to be a general feature of evolutionary
3 rescue in situations where it is most likely to occur. Conversely,
4 our message could be flipped to conclude that in cases where
5 extinction is likely, evolutionary rescue (should it occur) will
6 occur via hard selective sweeps.

7 Our model captures important aspects of population dynam-
8 ics and natural selection, although there are some limitations
9 that we feel should be addressed. First, departures from our an-
10 alytic assumptions occur in scenarios where mutations are rare
11 and when population decline is very slow, namely establishment
12 of one mutant lineage will affect the establishment of subsequent
13 mutant lineages because of density-dependent mutant growth
14 rates. Though we have chosen to not explicitly model this partic-
15 ular regime because it is not related to our primary focus on high
16 recurrent mutation and soft sweeps, it is noteworthy to consider
17 how populations can produce frequent rescue via hard sweeps
18 when population decline is slow (illustrated in Figure 3, Figure 4,
19 and Figure 5).

20 Second, another drawback of our analysis is that our measure
21 of P_{soft} is connected to the establishment of adaptive lineages
22 during the process of evolutionary rescue (inferred from knowl-
23 edge of the population composition after rescue or extinction)
24 and not specifically connected to a sample genealogy, as in Pen-
25 nings and Hermisson (2006a) and Wilson *et al.* (2014). This
26 means that our measure of P_{soft} will not necessarily capture how
27 the probability of observing a soft selective sweep depends on
28 lineage frequencies. It is possible that lower frequency lineages
29 could be missed in shallow samples. We can see how the ob-
30 served relationship between average heterozygosity (\bar{H}) in our
31 simulations (measured as the probability that all mutants sam-
32 pled immediately following rescue are not identical by descent)
33 and rescue probability has the same basic correlation as our
34 measure of $P_{\text{soft}}|P_{\text{rescue}}$ in Figure 7. There is lower sensitivity to
35 detect genetic diversity in such a shallow samples (sample size
36 = 2 in Figure 7), but in larger samples, the expected correlation is
37 virtually identical to the analytic expectation (sample size = 100
38 in Figure 7). We therefore highlight that empirical observations
39 of soft selective sweeps in rescued populations are still crucially
40 dependent on sample depth.

41 Finally, we note that in this paper we have only considered
42 the locus where the beneficial mutation that leads to rescue
43 can occur, and we have not considered any neutral loci in the
44 genome, whether linked to the selected locus or not. Whether or
45 not a selective sweep in a rescued population can be detected is
46 a question that deserves separate treatment, but it is likely that
47 selective sweeps will be very hard to detect if the population as
48 a whole goes through a severe bottleneck. This could mean that
49 in rescued populations, hard sweeps may be harder to detect
50 than soft sweeps because hard sweeps tend to occur when the
51 population bottleneck is more severe.

52 **The importance of genetic diversity in rescued populations**

53 In Orr and Unckless (2014), the authors discuss how the average
54 minimum population size that is reached during evolutionary
55 rescue is smaller for adaptation via *de novo* mutation than for
56 adaptation from standing genetic variation because of the de-
57 pendence on the waiting time for the first established mutant
58 (τ_1 in this paper). They posit that this may lead to lower genetic
59 diversity in populations rescued via *de novo* mutation than those
60 rescued from standing genetic variation, presumably because
61 a larger average minimum population size would reduce the

62 strength of genetic drift, increase the average population-scale
63 mutation rate, and provide more opportunities for recombina-
64 tion to generate diversity within the rescued population. How-
65 ever, this relationship between genetic diversity and the mode
66 of adaptation (from standing versus *de novo* variation) is not as
67 direct when adaptation is driven by soft sweeps. Adaptation
68 via soft sweeps may not drastically remove genetic diversity in
69 an adapting population (Pennings and Hermisson 2006b), as
70 might be expected in a hard sweep where only one lineage car-
71 ries the adaptive mutation. In rescue via soft sweeps, adaptive
72 mutations occur on different genetic backgrounds either before
73 the environmental shift (in adaptation from standing genetic
74 variation) or during the population decline after the environ-
75 mental shift (in adaptation via *de novo* mutation). The degree to
76 which each mode of adaptation reduces genetic variation will
77 depend on the number of genetic backgrounds on which the
78 adaptive mutation occurs. The number of different lineages
79 could even be larger for adaptation via *de novo* mutation if the
80 adaptive mutation is strongly deleterious before the environ-
81 mental shift (explicitly, if fewer mutants would be drifting in
82 deleterious mutation-selection balance than would establish dur-
83 ing the population decline). The number of adaptive lineages
84 could be higher for adaptation from standing genetic variation if
85 the adaptive mutation is already segregating on many different
86 genetic backgrounds before the environmental shift. In either
87 case, soft sweeps will play a significant role in preserving genetic
88 diversity in the adapting population.

89 There are multiple reasons why higher genetic diversity fol-
90 lowing evolutionary rescue might be an important consideration.
91 First, preserving genetic diversity that was present prior to the
92 environmental shift will be important to the future fitness of the
93 population following evolutionary rescue, especially in popu-
94 lations that cannot generate diversity quickly. If evolutionary
95 rescue occurs via soft selective sweeps, then some of this ances-
96 tral diversity will be maintained for future generations. Second,
97 post-rescue genetic diversity can be a useful proxy for measuring
98 how likely such a population was to adapt to an environmental
99 pressure. For example, genetic diversity in the viral population
100 after the emergence of drug resistance could be used to deter-
101 mine the efficacy of a drug used to treat a virus within a patient
102 in higher resolution than viral load alone because genetic diver-
103 sity is expected to correlate with the likelihood that treatment
104 failure occurred *a priori*. In other words, when treatment failure
105 is common P_{rescue} is highest, and when P_{rescue} is highest we
106 expect treatment failure to be driven by soft sweeps (Feder *et al.*
107 2016). This leads to higher genetic diversity in samples where
108 failure was common and driven by soft sweeps than in sam-
109 ples where failure was rare and driven by hard sweeps. Indeed,
110 others have found a correlation between treatment efficacy in
111 HIV and whether treatment failure occurred via hard or soft
112 sweeps that is in agreement with the theoretical results of this
113 paper (Feder *et al.* 2016). Knowledge of this expected correlation
114 may be broadly applicable to analysis of other types of drug-
115 resistant infections, such as malaria. This correlation between
116 genetic diversity and the likelihood of evolutionary rescue is
117 expected to decay over time in an asexual population as genetic
118 drift will eventually remove all but one lineage, so the timing of
119 the population sample will be critical to the assessment of the
120 likelihood of evolutionary rescue.

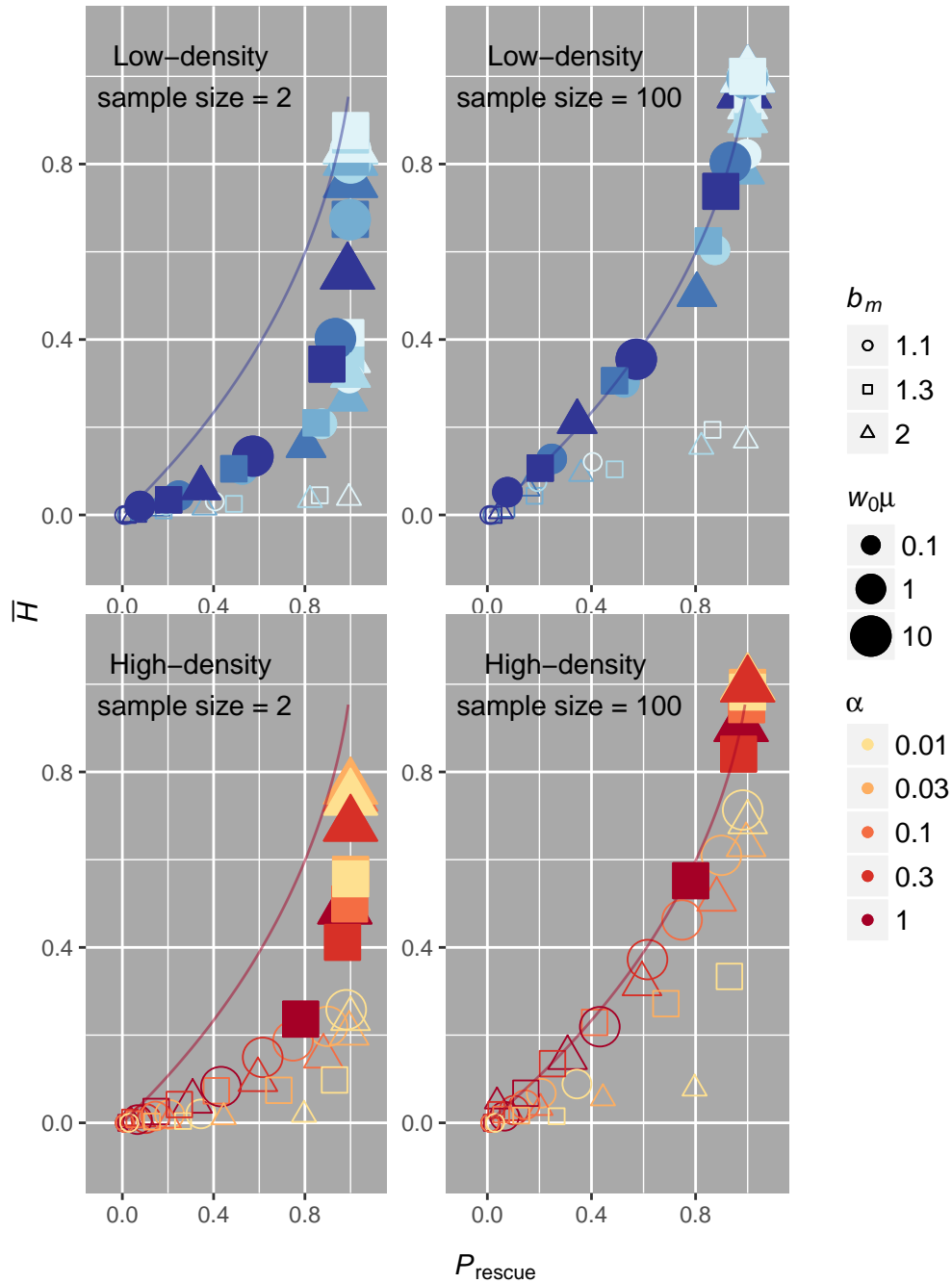


Figure 7 Mean heterozygosity from simulations of evolutionary rescue. Heterozygosity of the rescued population was calculated for each simulation and is equivalent to the probability that all sampled individuals do not come from a single mutant lineage. Plotted is the mean heterozygosity (H) averaged over all 1,000 simulations for each parameter set against the corresponding probability of rescue for each parameter set. Only parameter sets where our independence assumptions are valid ($w_0\mu \geq 1$ for low-density scenarios and $w^*\mu \geq 1$ for high-density scenarios) are shaded. Although the sample depth is as low as possible for a meaningful measure of genetic diversity in the sample size equal to two case, we still see a general correlation between genetic diversity and probability of rescue. The sensitivity with which one could distinguish rescue probability using genetic diversity is much smaller compared to the previous measure of P_{soft} where we knew the precise number of lineages following evolutionary rescue. However, the sensitivity is virtually identical for larger samples, as seen in the sample size equal to 100 case. For larger sample sizes, the values of mean heterozygosity inferred from our simulations more closely match our analytic predictions (colored lines). This indicates that deeper population samples will have better sensitivity toward identifying whether rescue was likely or unlikely in scenarios where it is otherwise difficult to ascertain the probability of rescue.

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